Claim 1 was rejected since citric and isocitric acids are not dicarboxylic acids. In the specification, applicants defined the term "dicarboxylic" acid to be "an organic acid having two or more carboxylic acid moieties (e.g. HOOC-R-COOH)" (page 2, lines 4 - 6 of specification). It is well-established that patent applicants may serve as their own lexicographer. Hormone Research Foundation, Inc. v. Genentech, Inc., 904 F.2d 1558 (Fed. Cir. 1991). Under such circumstances, applicants do not believe the term is indefinite as used. Of course, applicants will gladly consider any suggestion of the Examiner for substituting other terminology such as "polycarboxylic" or similar words if such terminology will be better understood.

Claim 1 was also considered indefinite in that "prevent" and "delay" do not have the same meanings. Applicants propose amending the claim to delete the "prevent" terminology.

Claims 7 and 10 were considered indefinite for use of the terminology "another gonadotropin". Applicants have amended the claims to state that a second gonadotropin is also included in the formulation (e.g FSH together with LH) in order to overcome the rejections under 35 USC 112. In view of the amendments, applicants request that the rejection be withdrawn.

Claim 13 was indefinite in having no antecedent basis for "said non-reducing sugar". Amended claim 13 depends from claim 2 having proper antecedent basis.

B. The claims and 35 USC 103-

Claims 1, 2, 6 - 8, and 10 - 14 stand rejected as being obvious over Kawaguchi et al. or Hamilton, Jr. et al. Applicants respectfully traverse the rejection.

The claims are to be amended, without prejudice, to include the limitation that the gonadotropin is of recombinant source. Basis for this amendment is set forth throughout the specification, in particular at page 4, lines 3 to 11, and in previous claim 14. It is therefore respectfully submitted that no new matter is being added. Previous claim 14 and the

previously submitted DECLARATION UNDER 37 CFR 1.132 (paragraph no. 8) both identify the problem associated with recombinant source gonadotropins, and the previous office action response identified the problem, so it is further submitted that no new issues are being raised by the amendment.

Applicants maintain that the invention cannot be considered obvious over Kawaguchi et al. and Hamilton, Jr. et al. because neither reference recognized the special problem associated with the stability of recombinantly produced proteins. Furthermore, even taking the teachings of these references into consideration, one of skill in the art would still have no reasonable expectation of success, and undue experimentation would be required in order to arrive at applicants' invention.

Although Hamilton, Jr. et al. and Kawaguchi et al. both mention that their respective proteins can be of recombinant source, they both in fact used natural source proteins in their examples and thus neither could have recognized the special problem associated with the stability of recombinant source proteins, let alone recombinant source gonadotropins. As previously stated, such very pure gonadotropins are inherently less stable than their natural source counterparts. (See, e.g. the specification at page 1, lines 20 to 30 and page 4, lines 3 to 10). The special problem associated with recombinant source gonadotropins was not and could not have been recognized by these references, since such proteins were not used, and thus the claims cannot be considered obvious over these references.

Furthermore, taking the teachings of these references into consideration, one of skill in the art would still have no reasonable expectation of success, and undue experimentation would be required in order to arrive at applicants' invention. Kawaguchi et al. mentions that sodium or potassium citrate, among a list of literally dozens of other compounds, can act to stabilize the glycoprotein erythropoietin. Concentrations of the specific organic salts useful for the task are not identified. No experimental results showing stabilization of erythropoietin

with the compounds are given in the examples. The patent does not even ultimately claim the use of such stabilizers, which brings into question whether or not the disclosure of Kawaguchi et al. is even sufficiently enabling to be used as a reference. Kawaguchi et al. merely mentions the compounds with numerous others. Accordingly, one of ordinary skill in the art would have to vary all parameters (e.g. choice of protein, its source, its purity, protein concentration, stabilizer selection from a long list, and stabilizer concentration) in order to come up with a possibly stable solution.

Kawaguchi et al. does not even disclose gonadotropin(s) or the criticality of a polycarboxylic acid salt for stabilizing gonadotropins. These differences were not considered critical however, since "a finding that one of the protein stabilizers taught by the prior art is better suited for the instant protein [than others] does not constitute unexpected and unobvious results". This reasoning ignores the fact that Kawaguchi et al.'s teachings concerning the stabilization of erythropoietin cannot be applied indiscriminately to the stabilization of recombinant source gonadotropins.

This shortcoming in the reasoning is demonstrated by comparing the entire disclosure of Kawaguchi et al. to the instant application. Kawaguchi et al. identifies maltose (column 1, line 67) and mannitol (column 2, line 1) as compounds which stabilize erythropoietin. As shown by applicants however, these "stabilizers" when tested with recombinant source gonadotropins actually <u>destabilize</u> them (see e.g. page 10, lines 1 to 6 of the specification and EXAMPLE I.A.). Destabilization of a protein is not a matter of "better suitability", it is a worsening of the problem to be solved.

Other teachings of Kawaguchi et al. are also not applicable to the case at hand. Kawaguchi et al. states that erythropoietin can be stabilized with sucrose alone. (Column 3, line 39). In contrast however, EXAMPLE I.B. of the specification shows that attempts to stabilize recombinant source gonadotropins with just

sucrose resulted in an unstable product with almost exclusive oligomer formation. Again the teachings of Kawaguchi et al. could not be applied indiscriminately to the case at hand. Just because a compound is listed as stabilizing one protein does not mean it will stabilize another. Urinary source erythropoietin is different from a recombinantly produced gonadotropin.

Kawaguchi et al. also does not identify salts of tartaric acid, aspartic acid, isocitric acid, and glutamic acid (claim 12), the correlation between ionic strength and recovery (claim 11 and FIG. 1 of specification), the use of trehalose (claim 13), and the stabilization of more than one gonadotropin (claim 10).

In view of these differences, Kawaguchi et al. cannot be said to make applicants' invention obvious.

Hamilton, Jr. et al. discloses the stabilization of pituitary source growth hormone by non-reducing sugars and various other compounds, including choline bitartrate tricholine citrate, and glutamate salts. As Hamilton, Jr. et al. so poignantly points out "the fact a particular stabilizer is effective with a particular protein does not necessarily mean that the particular stabilizer is appropriate for the stabilization of [another protein]." (Column 1, line 65 to column 2, line 1). This observation is in line with the general rule that "in arts such as chemistry it is not obvious from the disclosure of one species [i.e. one hormone or protein], what other species will work". MPEP 706.03(z).

This is only reasonable since different proteins have differing molecular weights, isoelectric points, solubilities, glycogen portions, stabilities, sources, etc., and what is known about one cannot predictably be applied to another. In the instant case, growth hormone is a single polypeptide with a molecular weight of about 21,500 and consists of 191 amino acids. In contrast, gonadotropins are glycoproteins with molecular weights of about 25,000 (FSH) and 40,000 (LH) consisting of two nonidentical, noncovalently linked subunits, the α and β chains. Stabilization of a compound which is a single polypeptide chain

is not the same thing as stabilization of a larger polypeptide with non-covalently linked subunits as the compounds are too different.

Although the Examiner admits that Hamilton, Jr. et al. does not disclose a lyophilized product, applicants were still requested to supply evidence showing that Hamilton's dry hormone was not obtained by lyophilization. The best evidence of this is the Hamilton, Jr. et al. reference itself. Freeze-drying or lyophilization is not disclosed or even implied. In fact, in the described "dry state", the Hamilton, Jr. et al. composition is a "dry mixture comprising solid growth hormone and solid stabilizer." (Column 2, lines 58 - 65 of Hamilton, Jr. et al.). "The preparation of the stabilized growth promoting formulations containing the stabilizer and the growth hormone may be by simple mechanical mixing". (Column 4, lines 65 - 67). "In another embodiment, the stabilizer and growth hormone can be wet or dry mixed to provide a solid formulation which is particularly suited for implants." (Column 5, lines 14 - 17 of Hamilton, Jr. et al.). Example 3 of the reference describes that the growth hormone and stabilizers were dry mixed. (Column 10, lines 56 - 57 of Hamilton, Jr. et al.). Clearly the reference does not disclose applicants' invention which involves pre-mixing a polycarboxylic acid stabilizer with a recombinant source gonadotropin and then freeze-drying to form a stable lyophilisate. It merely discloses a dry mixture.

Furthermore, the fact that protein lyophilization is known does not change the fact that Hamilton, Jr. et al. does not disclose the lyophilization of an aqueous solution containing a recombinant source protein and polycarboxylic acid salt stabilizer or that such a lyophilisate is exceedingly stable.

As also acknowledged by the Examiner, Hamilton, Jr. et al. does not teach gonadotropins or the amounts of stabilizers in the combination.

Furthermore, as previously stated with regard to the Kawaguchi et al. reference, the teachings of Hamilton, Jr. cannot be

readily applied to the present invention. Contrary to what Hamilton, Jr. et al. reports, non-reducing sugars by themselves are insufficient to stabilize recombinant source gonadotropins. Hamilton, Jr. et al. encountered a similar problem with prior art polyols, as not all were found to stabilize growth hormones. (Column 4, lines 3 - 6 and column 9, line 67 to column 10, line 33). The stability of various proteins or even the same proteins from various sources (see e.g. the earlier submitted DECLARATION wherein hCG from urinary sources is inherently more stable than hCG of recombinant source) with various stabilizers is just insufficiently predictable to make the invention obvious.

Under these circumstances, applicants believe that the claims should not be rejected as being obvious over Hamilton, Jr. et al., Kawaguchi et al. or both of them.

The rejection of claim 13 as being obvious over Hayashi et al., Iwasa et al. or Block et al. is considered adequately addressed by the response to the Hamilton, Jr. et al. and Kawaguchi et al. references. None disclose a stabilized lyophilisate containing a recombinant source gonadotropin and polycarboxylic acid salt.

The criticality of the limitation in claim 14 was thought unclear. Since applicants have amended the other claims to include the limitation, without prejudice to the pursuit of the subject matter of the earlier claims in a later related application, and have explained the relevancy of the limitation with respect to the prior art, applicants believe that the question has been adequately addressed.

Applicants' way of stabilizing recombinant source gonadotropins could not have been predicted by the prior art. What works for one protein will not necessarily work for another as is clearly demonstrated by the art of record, and is generally accepted in the field, including the generally accepted patent law field.

In view of the amendments and remarks, applicants believe the application to be in condition for allowance. Favorable action is solicited.

Should the Examiner consider that a conference would be helpful in advancing the prosecution of this application, the Examiner is invited to telephone Applicants' attorney at the number below. In the event any fees are required with this paper, please charge our Deposit Account No. 02-2334, for which purpose duplicate copies are enclosed.

Respectfully submitted,

Donna Bobrowicz
Attorney for Applicants
Registration No. 32,196

AKZO PHARMA
1330-A Piccard Drive
Rockville, Maryland 20850-4373
Tel: (301) 258-5200

DB:ms

62demere.amd